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REVIEW article

# Targeting the Wnt/β-catenin axis through sclerostin inhibition in postmenopausal osteoporosis: Translational advances and safety perspectives

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**Abstract:** Post menopausal osteoporosis is a chronic metabolic bone disorder characterised by decreased bone mineral density and increased risk of fracture due to estrogen deficiency. This estrogen deficiency will reduce osteogenesis and increase osteoclast-mediated bone resorption, leading to an imbalance in bone remodelling. The Wnt/β-catenin signalling pathway plays an important role in regulating bone formation by promoting osteoblast differentiation and inhibiting resorption. Sclerostin, produced by osteocytes, inhibits and binds to LRP5/6 co-receptors in this pathway and suppresses bone formation. This review summarises the molecular mechanisms of Wnt/β-catenin signalling and the role of sclerostin in the pathogenesis of postmenopausal osteoporosis. It also explains recent therapeutic advances in anti-sclerostin therapy, such as Romosozumab, which restores Wnt signalling by enhancing bone formation and reducing bone resorption. Various clinical studies suggested a significant increase in bone mineral density and a reduction in fracture risk, but these are also associated with cardiovascular effects like stroke and myocardial infarction. Future research should focus on biomarker-guided therapy, precision medicine, and novel Wnt pathway modulators to optimise treatment efficacy and safety in the management of postmenopausal osteoporosis.

## Introduction

Postmenopausal Osteoporosis is an age-related condition in women who experience an increased risk of broken bones, reduced cortical level and cancellous bone thickness, and a reduction in bone mineral density (BMD) [1]. After menopause, there will be a decrease in the level of oestrogen, which leads to the loss of bone [2, 3]. The CDC report showed 5.6% increase in osteoporosis in women compared to reports from 2008 and 2018. There is a 50.4% prevalence of osteoporosis in postmenopausal women as per the Reyes Balaguer and Moreno Olmos Study [4]. In Pharmacological Management of Osteoporosis in Postmenopausal Women, the Endocrine Society said that treatment with bisphosphonates or denosumab decreases the risk of fracture in postmenopausal women with osteoporosis [5]. Long-term treatment with bisphosphonates is linked with rare but serious adverse effects like atypical femoral fractures and osteonecrosis of the jaw, and denosumab has a rebound effect [6, 7]. Selective estrogen receptor modulators are less effective and may increase the risk of venous thromboembolism and vasomotor symptoms [8]. Wnt/β-Catenin Pathway promotes bone formation by osteoblast differentiation and suppresses bone resorption. Wnt/β-Catenin Pathway increases the level of β-catenin in the cytoplasm and leads to gene transcription [9]. In postmenopausal women due to estrogen deficiency, there will increase in the level of sclerostin, which enhances the differentiation of osteoclasts and leads to an imbalance between bone resorption and bone formation by binding to LRP5/6 co-receptors [10].

Sclerostin is the negative regulator of bone formation, which is encoded by the SOST gene. It is produced by the mature osteocytes, inhibiting osteoblast differentiation and bone formation [11]. Anti-Sclerostin Therapy acts by specifically binding to and neutralising circulating sclerostin. In postmenopausal osteoporosis, sclerostin will bind to LRP5/6 co-receptors, which inhibit the activation of the canonical Wnt/β-catenin pathway. Targeting the Wnt/β-Catenin Pathway promotes osteoblast differentiation, leading to bone formation, inhibits the resorption, and can be used to treat postmenopausal osteoporosis [12]. This review explores Targeting the Wnt/β-Catenin Axis Through Sclerostin Inhibition in Postmenopausal Osteoporosis.

*Overview of bone remodelling:* Bone remodelling is a continuous lifelong process where old and damaged bone is resorbed and replaced by new bone. It maintains the integrity of the skeletal system and maintains $Ca^{2+}$ and phosphate balance (homeostasis). Osteoclasts, osteoblasts, and osteocytes play an important role in the process of bone remodelling [13]. Osteoclasts derived from hematopoietic stem cells break down bone matrix by a combination of lysosomal enzymes and hydrogen ions and are involved in bone resorption [14]. Osteoblasts are derived from mesenchymal stem cell is responsible for synthesizing and mineralizing the bone matrix, leading to bone formation and providing structural support [15]. Osteocytes are mature bone cells present within the bone matrix, and their role is to send a signal for the recruitment of osteoclasts during damage or mechanical stress and thereby regulate osteoclasts to release signalling molecules such as RANKL and sclerostin [16]. Coordination between osteoclasts and osteoblasts is required for the destruction and reconstruction of new bone, which is referred to as basic multicellular units (BMUs) [13].

Bone remodelling takes place in 5 sequential phases, namely activation, resorption, reversal, formation, and mineralization. Mechanical stress or damage to the bone is recognized by osteocytes, it recruits osteoclast precursors at the damage site in the activation phase. Osteoclasts will attach to the bone surface and create a resorption pit. Formation of new bone is facilitated by mononuclear cells on its surface and recruits osteoblast precursors, which differentiate to synthesize new bone matrix called osteoid, and these osteoids are converted into mature bone in the mineralization phase, as explained **(Figure 1)** [17].

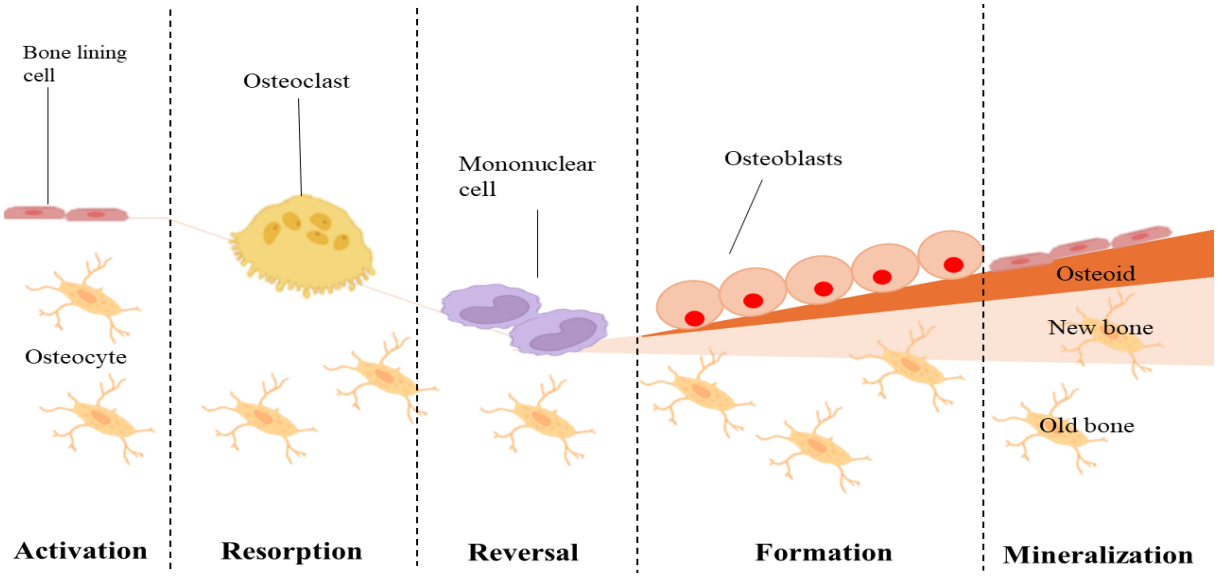


**Figure 1:** Physiology of bone remodelling

*The Wnt/β-catenin signalling pathway:* The Wnt/β-catenin signalling pathway is also called the canonical Wnt signalling pathway. It promotes bone formation by stimulating osteoblast differentiation and suppressing bone resorption [18].

*Canonical Wnt signalling mechanism:* When the Wnt ligand is absent, Axin, APC, GSK-3β, and CK1 form a complex also called the destruction complex, which captures β-catenin and phosphorylates it by GSK-3β. CK1 leads degraded of β-catenin by ubiquitination, thus TCF/LEF will bind to the transcriptional repressor, such as Groucho, and

suppress gene transcription. In the presence of Wnt ligand, it binds to two receptor that is Frizzled receptor and the LRP5/6 co-receptor, leading the signalling cascade is activation. Frizzled receptor recruits Axin, GSK3β, and Dishevelled (Dvl). Dvl inhibits the formation of the destruction complex, thus preventing the phosphorylation of β-catenin, which leads to increased concentration of β-catenin in the cytoplasm, which translocates into the nucleus and binds to transcription factors TCF/LEF and activates gene transcription, as shown in **Figure 2** [9].

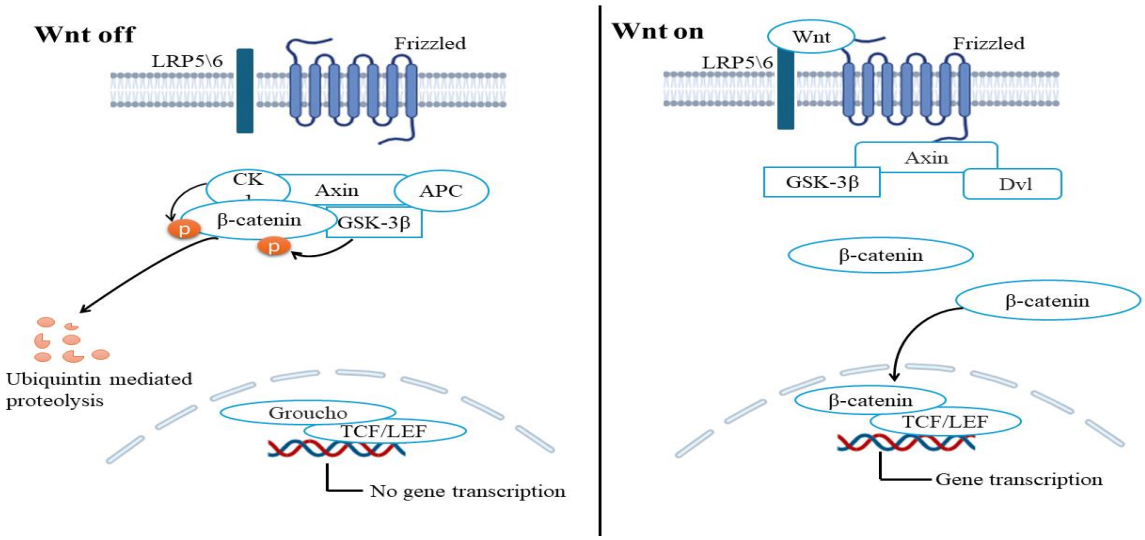


**Figure 2:** Mechanism of the canonical Wnt signalling pathway

*Role of LRP5/6 Co-receptors:* LRP5/6 is a low-density lipoprotein receptor-related 5/6 protein that plays an essential role in the Wnt/β-catenin signalling pathway. They facilitate the formation of the Wnt-Frizzled complex, which lead recruits axin, thus inhibiting the formation of the destructive complex, inhibiting the phosphorylation of β-catenin, promoting the translocation of β-catenin, hence activating the TCF/LEF-dependent gene transcription. Any mutation in LRP5/6 leads to osteogenesis imperfecta, bone fragility, and high bone mass syndromes. They regulate bone density and skeletal strength, and binding of sclerostin blocks Wnt ligand and reduces bone formation [9].

*β-catenin stabilization and gene transcription:* In the absence of Wnt, β-catenin is degraded by axin, APC, GSK-3β, and CK1 complex. The phosphorylation of β-catenin leads to ubiquitin-mediated proteolysis, thus leading to a decrease in the concentration of β-catenin in the cytoplasm; hence, gene transcription will be inhibited [19]. Upon binding to Wnt to Frizzled and LRP5/6 receptors, axin is recruited to the membrane and inhibits the formation of the axin, APC, GSK-3β, CK1 complex. β-catenin will not degrade, thus there will be an increase in the amount of β-catenin in the cytoplasm. The β-catenin moves into the nucleus and binds to transcription factor TCF/LEF, which binds to the target DNA, leading to gene transcription. These genes are required for osteoblast differentiation and bone formation. Some important genes are RUNX2, osterix, cyclin D1, c-Myc, and ALP (Alkaline phosphatase). Activation leads to differentiation of mesenchymal stem cells into osteoblasts and leads to bone formation [9].

*Regulation of osteoblast differentiation:* The Wnt/β-catenin signalling pathway is a regulator of osteoblastogenesis. Mesenchymal stem cells present in bone marrow can be differentiated into osteoblasts, adipocytes, and chondrocytes [20]. Binding β-catenin to the transcription factor TCF/LEF activates the transcription factors such as RUNX2, osterix, that are required for osteoblast differentiation [9]. β-catenin suppresses the activation of PPARγ and C/EBPα, which are required for activation in adipocytes, thus enhancing bone formation. Wnt/β-catenin signalling pathway activates cyclin D1 and c-Myc, thus promoting cell growth and cell division [21]. Wnt/β-catenin signalling stimulates OPG synthesis and inhibits bone resorption, thus reducing osteoclast formation [22].

*Sclerostin and its mechanism:* Sclerostin is a glycoprotein with a weight of ~22–24 kDa, which is encoded by the SOST gene. It is a negative regulator of bone formation. It is produced by the mature osteocytes, inhibiting osteoblast differentiation and bone formation. Sclerostin will increase with aging and in estrogen deficiency. The main function is to inhibit the Wnt/β-catenin signalling pathway [11]. It will bind to the LRP5/6, which is a co-receptor required for the binding of Wnt ligand, along with the Frizzled receptor. Thus, prevent the binding of Wnt to the receptor complex. This leads to the formation of a destruction complex, which phosphorylates and degrades the β-catenin. Leads to loss of stability β-catenin, and there will be no translocation of β-catenin into the nucleus, suppressing gene transcription and activation of genes such as RUNX2, osterix, ALP, which are required for bone formation and osteoblast differentiation [9, 23]. SOST gene mutation leads to loss of function, causing high bone mass disorders such as Sclerosteosis and Van Buchem Disease [24]. Sclerostin indirectly enhances bone resorption by the RANK/RANKL/OPG axis. Wnt/β-catenin pathway suppresses RANKL and stimulates OPG in osteoblasts. Sclerostin reduces the Wnt signalling, thus promoting osteoclastogenesis by increasing the RANKL expression and decreasing the OPG, which acts as a decoy for RANKL. There will be reduced osteoblast differentiation and bone formation. RANKL/OPG ratio increases due to suppression of Wnt signalling. In osteoclast precursors, a greater number of RANKL binds to RANK receptors, which leads to the formation of a mature osteoclast and increases resorption of the bone. It will directly decrease bone formation and indirectly increase bone resorption by inhibiting Wnt signalling and increasing the RANKL/OPG ratio, respectively [25].

*Pathophysiology in postmenopausal osteoporosis:* Postmenopausal osteoporosis is defined by an increase in osteoclast differentiation, bone resorption, and rapid bone loss due to oestrogen deficiency, especially in pre- and postmenopausal women. Estrogen deficiency causes suppression of the Wnt/β-catenin signalling pathway by increasing the levels of Sclerostin, which enhances the differentiation of osteoclasts and leads to disruption of the tightly regulated balance between bone resorption and bone formation, as explained in **Figure 3** [10].

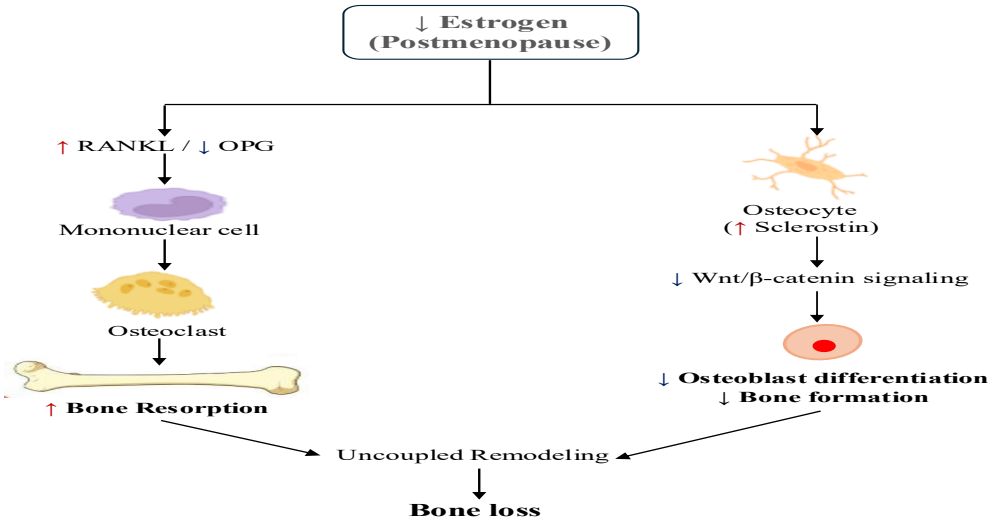


**Figure 3:** Estrogen deficiency-induced remodelling imbalance in postmenopausal osteoporosis

oestrogen plays an important role in maintaining normal bone balance by regulating osteoclasts and osteoblasts. In normal conditions, estrogen decreases osteoclast activity and formation (osteoclastogenesis), promotes osteoclast apoptosis, osteoblast survival, and bone formation, which is required for osteoblast differentiation [26]. Reducing oestrogen levels after menopause reduces the protective effects of oestrogen on bone function. Oestrogen deficiency enhances the production of RANKL and reduces the production of OPG [27]. It reduces the Wnt/β-catenin signalling, thus reducing the binding of β-catenin to TCF/LEF transcription factor and inhibiting transcription of osteogenic genes such as RUNX2 and osterix, which are required for osteoblast differentiation. It increases the bone resorption and decreases the bone formation simultaneously, which leads to disruption of the balance of the remodelling cycle, leading to increased bone loss [9, 10].

Reduced levels of estrogen in postmenopausal women leads reduce the suppression of sclerostin, and hence the levels of sclerostin will increase. This increase in the level of sclerostin will block the Wnt/β-catenin pathway, leading to decreased osteoblast differentiation and bone formation [27]. After menopause, there will be an increase in the RANKL/OPG ratio, and the osteoclast activity is increased due to estrogen deficiency, thus leading to enhanced bone resorption [27, 28]. Also, Wnt/β-catenin signalling is suppressed due to an increase in the level of Sclerostin, which leads to reduced osteoblast differentiation and activity, finally leading to reduced bone formation [23]. Imbalance in the remodelling leads to loss of trabecular bone, thinning of cortical bone, increased cortical porosity, decreased bone mineral density (BMD), and reduced bone strength. As a result, bones become more fragile and susceptible to fractures, particularly at the spine, hip, and wrist [29]. So, inhibition of sclerostin can restore Wnt signalling, stimulate osteoblast activity, and enhance the bone mass in postmenopausal women [30].

*Translational development of sclerostin inhibitors:* Researchers found that sclerostin plays an important role in the inhibition of bone formation, thus anti-sclerostin therapy can be used as a targeted therapy in postmenopausal osteoporosis. Development in the field of molecular biology and antibody engineering led to the discovery of pharmacological agents that can neutralise sclerostin, restore Wnt/β-catenin signalling, and balance between bone formation and resorption in postmenopausal osteoporosis [12].

*Mechanism of action of anti-sclerostin therapy:* Anti-sclerostin therapy acts by binding and neutralising existing sclerostin in the system. In postmenopausal osteoporosis, sclerostin will bind to LRP5/6 co-receptors and inhibit the activation of the Wnt/β-catenin pathway. This leads to suppression of osteoblast differentiation and bone formation [12]. In anti-sclerostin therapy, Wnt ligands can bind to LRP5/6 receptor and form a complex, because it inhibits sclerostin, which leads to the cytoplasm stabilisation and accumulation of β-catenin, leading to the translocation of β-catenin into the nucleus and will interact with TCF/LEF transcription factors, resulting in the activation of osteogenic genes like RUNX2 and osterix. Thus, increases the differentiation, maturation, and activity of the osteoblast, leading to enhanced bone formation. Also, Wnt signalling will increase OPG expression, which inhibits RANKL-mediated osteoclastogenesis, thus reducing bone resorption. Therefore, anti-sclerostin therapy restores bone remodelling balance [31].

*Development of monoclonal antibodies:* Scientists have developed several humanised monoclonal antibodies for targeting sclerostin. It has a high affinity to sclerostin and specifically will bind to sclerostin, thus preventing sclerostin binding to LRP5/6 receptors [32]. Romosozumab is the most recent anti-sclerostin antibody discovered, which showed a significant increase in bone density and reduced the risk of fracture in postmenopausal women. The development of monoclonal antibodies shifted from traditional antiresorptive therapies toward biologic agents that increase bone formation by targeting the Wnt/β-catenin pathway [33].

*Dual anabolic and antiresorptive effects:* Antisclerostin therapy has a dual mechanism of action, unlike conventional antiresorptive drugs that primarily reduce osteoclast activity. Sclerostin inhibitors will stimulate bone formation by increasing osteoblast differentiation and function, and also reduce bone resorption through an increase in OPG expression and reduction in osteoclastogenesis. This dual action rapidly increases bone mineral density, improves trabecular and cortical bone, and enhances bone strength. The combination of anabolic and antiresorptive effects of sclerostin inhibitors distinguishes itself from other osteoporosis treatments as an important therapeutic option in postmenopausal osteoporosis [34].

Romosozumab is a humanized monoclonal antibody sclerostin inhibitor that is used to treat osteoporosis in postmenopausal women who are at an increased risk of fracture. It showed significant enhancement in bone mineral density and reduction in fracture risk in postmenopausal osteoporosis as per certain clinical evidence. Several studies, such as FRAME and ARCH, confirm that romosozumab has high efficacy compared to placebo and other conventional antiresorptive therapies. But several cardiovascular adverse events were noted, indicating the requirement of post-marketing surveillance as mentioned in **(Table 1)** [35-39].

**Table 1:** Clinical trials of sclerostin inhibition in postmenopausal osteoporosis

| Study | Key findings | ADR | Efficacy |
|---|---|---|---|
| **FRAME Trial (Fracture Study in Postmenopausal Women with Osteoporosis) [35]** | Romosozumab treatment for 12 months significantly increases bone mass and reduces the incidence of new vertebral fractures compared with placebo. Continued therapy with denosumab helped maintain these gains in bone strength. | Injection-site reactions, arthralgia, headache, mild hypocalcaemia; overall tolerability similar to placebo. | ~73% reduction in new vertebral fractures at 12 months; significant increase in lumbar spine BMD (~13%). |
| **ARCH Trial (Active-Controlled Fracture Study) [36]** | Sequential therapy using romosozumab followed by alendronate showed superior therapy in the prevention of fractures compared with alendronate alone in high-risk postmenopausal women. | Arthralgia, injection site reactions, headache; slightly higher incidence of cardiovascular events reported in the romosozumab group. | ~48% reduction in vertebral fractures, ~27% decrease in clinical fractures, and ~38% decrease in hip fractures. |
| **STRUCTURE Trial [37]** | In women previously treated with bisphosphonates, romosozumab produced greater improvements in bone density compared with teriparatide, particularly at the hip. | Injection site reactions, mild hypercalcemia or hypocalcemia, and musculoskeletal pain. | Total hip BMD increased by ~2.6% with romosozumab while decreasing slightly with teriparatide. |
| **Phase II Dose-Finding Trial [38]** | Different doses of romosozumab were evaluated, demonstrating rapid stimulation of bone formation markers and significant increases in BMD compared with placebo and alendronate. | Injection site reactions, transient decreases in serum calcium, and mild flu-like symptoms. | Lumbar spine BMD increased up to ~11% within 12 months, depending on dose. |
| **BRIDGE Trial (Men with Osteoporosis) [39]** | Romosozumab significantly improved bone mineral density in men with osteoporosis compared with placebo, suggesting similar anabolic effects across sexes. | Injection site reactions, headache, nasopharyngitis; slightly increased cardiovascular events observed. | Lumbar spine BMD increased by ~12% and total hip BMD by ~2.5% after 12 months. |

*Safety and risk assessment:* Although monoclonal antibodies like romosozumab showed a significant effect in clinical trials, there have been reports of several adverse effects [40]. The most common side effects include headache, fatigue, arthralgia, pain at the site of injection, and hypersensitivity reactions. Also, transient hypocalcaemia has been observed in patients with vitamin D deficiency or low levels of calcium, which highlights that these conditions should be corrected before treatment with romosozumab [41, 42]. Studies-like ARCH suggested that there is a higher incidence of cardiovascular risk, such as myocardial infarction and stroke, in patients treated with romosozumab when compared to alendronate, whereas in the FRAME Trial, cardiovascular events were not observed, leaving the uncertain causal relationship [36, 37]. Sclerostin is also expressed in vascular tissues, where it is regulated by the Wnt signalling pathway in vascular smooth muscle cells, which leads to vascular calcification and remodelling. Inhibition of sclerostin by romosozumab will increase the Wnt/β-catenin signalling pathway, which leads to arterial calcification or will affect the plaque stability in patients with pre-existing cardiovascular disease [43]. Due to this, regulatory authorities like the USFDA and EMA recommended that romosozumab should not be used in patients with a recent history of myocardial infarction or stroke. Regulatory guidelines recommend that the drug be mainly used by postmenopausal women with severe osteoporosis or very high fracture risk who do not have a previous history of cardiovascular disease, followed by antiresorptive therapy [44].

*Emerging Wnt pathway targets:* Dickkopf-1 (DKK-1) inhibition, Notum inhibitors are some examples of emerging targeting therapies for the Wnt pathway, where they will inhibit DKK-1 and Notum, respectively, thereby increasing Wnt signalling, leading to enhanced bone formation. Small-molecule Wnt modulators will regulate the components of the signalling cascade, and biologic approaches, including engineered antibodies, recombinant proteins, and gene therapy, will selectively activate Wnt signalling in bone tissue, as mentioned in **Table 2** [45-49].

**Table 2:** Emerging targets for the Wnt pathway

| Targets | Mechanism of action | Therapeutic effects |
|---|---|---|
| **Dickkopf-1 (DKK-1) Inhibition [45]** | DKK-1 normally blocks Wnt signalling by inhibiting the binding of Wnt ligands to LRP5/6 receptors. Inhibiting DKK-1 restores Wnt/β-catenin signalling and enhances osteoblast differentiation. | Increased bone formation, improved bone mineral density, and potential reduction in fracture risk. |
| **Notum inhibitors [46]** | Notum suppresses Wnt signalling by removing lipid modifications from Wnt proteins, which reduces their activity. Inhibiting Notum leads to activation of Wnt ligands and maintains signalling. | Stimulation of osteoblast activity and promotion of bone formation. |
| **Small-molecule Wnt modulators [47]** | These compounds regulate components of the Wnt signalling cascade, such as stabilising β-catenin or blocking pathway inhibitors. | May increase bone formation and improve skeletal strength with potential oral drug formulations. |
| **Future biologic approaches [48, 49]** | Includes engineered antibodies, recombinant proteins, and gene-targeted therapies designed to selectively activate Wnt signalling in bone tissue. | Highly targeted therapy for bone formation while minimising systemic side effects. |

*Future perspective:* Emerging research in postmenopausal osteoporosis targeting the Wnt/β-catenin signalling pathway focuses on safer and more personalised therapy. Biomarker-guided therapy may help researchers to use bone turnover markers like P1NP and CTX to identify patients who are most likely to benefit from romosozumab [50]. Treatment selection can be further optimised by integrating Precision medicine with genetic factors, assessment of fracture risk, and patient-specific characteristics. Cardiovascular disease associated with the sclerostin inhibitors to modulate the Wnt pathway can be studied through post-marketing surveillance and extended clinical studies. Ongoing clinical studies can also evaluate new Wnt pathway modulators, biologic therapies, and treatment strategies to increase bone density, reduce the risk of fracture, and improve patient outcomes in post-menopausal women [51].

*Conclusion:* Sclerostin is a potential inhibitor of Wnt/β-catenin signalling and regulates bone formation. Estrogen deficiency in postmenopausal women leads to overexpression of sclerostin, thereby leading to an imbalance in bone formation and resorption. Antisclerostin therapy is used to manage post-menopausal osteoporosis by inhibiting sclerostin in the Wnt/β-catenin signalling pathway. Sclerostin inhibitors increase osteoblast activity and bone mineral density, and significantly reduce fracture risk, but they are associated with serious cardiovascular events. For the rational use of Sclerostin inhibitors, various regulatory authorities, such as the USFDA and EMA, provided guidelines to ensure the safe and effective use of the drug. Future research should focus on biomarker-guided therapy, precision medicine, and novel Wnt pathway modulators to optimise treatment efficacy and safety in the management of postmenopausal osteoporosis.

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